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Diagnosis and treatment of chronic bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome: a consensus guideline

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Abstract

Objectives

To improve awareness and recognition of chronic bacterial prostatitis (CBP) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) among non-specialists and patients. To provide guidance to healthcare professionals treating patients with CBP and CP/CPPS, in both non-specialist and specialist settings. To promote efficient referral of care between non-specialists and specialists and the involvement of the multidisciplinary team (MDT).

Patients and Methods

The guideline population were men with CBP or CP/CPPS (persistent or recurrent symptoms and no other urogenital pathology for ≥3 of the previous 6 months). Consensus recommendations for the guidelines were based on a search to identify literature on the diagnosis and management of CBP and CP/CPPS (published between 1999 and February 2014). A Delphi panel process was used where high-quality, published evidence was lacking.

Results

CBP and CP/CPPS can present with a wide range of clinical manifestations. The four main symptom domains are urogenital pain, lower urinary tract symptoms (LUTS – voiding or storage symptoms), psychological issues and sexual dysfunction. Patients should be managed according to their individual symptom pattern. Options for first-line treatment include antibiotics, α-adrenergic antagonists (if voiding LUTS are present) and simple analgesics. Repeated use of antibiotics, such as quinolones, should be avoided if there is no obvious symptomatic benefit from infection control or cultures do not support an infectious cause. Early use of treatments targeting neuropathic pain and/or referral to specialist services should be considered for patients who do not respond to initial measures. An MDT approach (urologists, pain specialists, nurse specialists, specialist physiotherapists, general practitioners, cognitive behavioural therapists/psychologists, and sexual health specialists) is recommended. Patients should be fully informed about the possible underlying causes and treatment options, including an explanation of the chronic pain cycle.

Conclusion

Chronic prostatitis can present with a wide variety of signs and symptoms. Identification of individual symptom patterns and a symptom-based treatment approach are recommended. Further research is required to evaluate management options for CBP and CP/CPPS.

Keywords: guidelines, chronic bacterial prostatitis, chronic prostatitis with chronic pelvic pain syndrome, prostatitis

Introduction

Go to:

Prostatitis is a common condition, with 35–50% of men reported to be affected by symptoms suggesting prostatitis during their lifetime 1, 2. Based on a population of >10 600 participants, a systematic review found an 8.2% prevalence of prostatitis symptoms 3.

The symptomatic, chronic forms of prostatitis as defined by the USA National Institutes of Health (NIH; Box 1) 3, are chronic bacterial prostatitis (CBP; NIH category II) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS; NIH category III). Despite having a significant negative impact on patients' quality of life (QoL) 4 and presenting diagnostic and therapeutic challenges for physicians, CBP and CP/CPPS have received relatively little attention in the literature, in comparison with other urological conditions 2. The absence of robust and clear epidemiological data may also reflect the lack of a uniform definition and the overlap of symptoms with other conditions, such as benign prostatic enlargement (BPE) and prostate cancer.

Box 1

NIH classification and definition of the categories of 'prostatitis' 3

NIH classification	Definition
I: Acute bacterial prostatitis	Acute infection of the prostate gland
II: Chronic bacterial prostatitis (CBP)	Chronic or recurrent infection of the prostate
III: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)	No demonstrated infection
IIIa: Inflammatory CPPS*	White blood cells in semen and/or EPS or VB3 after prostatic massage
IIIb: Non-inflammatory CPPS*	No white cells in semen/EPS/VB3
IV: Asymptomatic inflammatory prostatitis	No subjective symptoms detected Inflammation shown either by prostate biopsy or the presence of white cells in EPS/semen during evaluation for infertility or other disorders

EPS, expressed prostatic secretions; VB, voided bladder; VB3, post-prostatic massage voided bladder urine.
*During CP/CPPS, it is possible for patients to switch between the two subcategories (IIIa and IIIb), but this has little effect on subsequent clinical management.

Guideline and Objectives

Go to:

A Prostatitis Expert Reference Group (PERG) was convened by Prostate Cancer UK, to develop consensus guidelines to improve the diagnosis and management of CBP and CP/CPPS. The main objectives of the guidelines were to:

- Provide guidance to healthcare professionals treating patients with CBP and CP/CPPS, both in non-specialist and specialist settings.
- Improve awareness and recognition of these conditions among non-specialists and patients.
- Promote efficient referral of care between non-specialists and specialists and the involvement of the multidisciplinary team (MDT).

Methods

Go to:

PERG

PERG members (Appendix S1) were invited from a network of clinical experts in the urology field across a broad range of disciplines, including primary care, urology (medical and nurse specialists), pain medicine, physiotherapy and psychology, as well as patient representatives. Also included were a technical team from Prostate Cancer UK and Hayward Medical Communications, with a background in communication, policy development and evidence research. The PERG met several times during the guideline development process, to discuss objectives and scope of the guidelines, assess the literature review outcomes and formulate the guidelines.

Literature Search

A search was conducted to identify literature on the diagnosis and management of CBP and CP/CPPS published between 1999 and 7 February 2014. The primary database searched was Medline (via PubMed); additional sources included the Cochrane Library and professional guideline groups, including the National Institute for Health and Care Excellence (NICE) and the European Association of Urology (EAU) (Appendix S2). For the full literature search protocol see Appendix S3. References used in the guideline were graded according to the Oxford Centre for Evidence-based Medicine (OCEBM) Levels of Evidence (Table 1) 5.

Table 1

Levels of evidence. Modified from OCEBM Levels of Evidence Working Group 5

Level	Source of evidence
1	Meta-analysis of randomised trials
2	At least one well-designed randomised controlled study
3	Non-randomised controlled cohort or follow-up study
4	Case series, case-control studies, or historically controlled studies
5	Mechanism-based reasoning, expert committee reports or opinions or clinical experience of respected authorities

Delphi Panel

Due to the limited number of published randomised controlled trials (RCTs) in CBP and CP/CPPS, the PERG concluded that the guideline would benefit from input from a supporting panel of experts. Thus, a web-based Delphi panel process was conducted to form consensus recommendations where high-quality, published evidence was found to be lacking. This anonymous and iterative group technique is designed to gather individual opinions from experts and transform these into a group consensus 6. The Delphi panel comprised three questionnaire rounds via Survey Monkey® (for the survey questions see Appendix S4). Where consensus (agreement of ≥70% of respondents) was not achieved, input was obtained from the PERG and supporting technical team.

Results

Go to:

The Delphi panel survey was circulated to 58 participants (GPs, urologists, pain specialists, nurse specialists, physiotherapists, cognitive behavioural specialists and sexual health specialists), of whom 35 (60%), 29 (50%) and 26 (45%) responded to the first, second and third rounds, respectively. All treatment recommendations that achieved consensus from the PERG or Delphi panel are shown below in bold type.

Signs and Symptoms

The wide range of clinical manifestations of CBP and CP/CPPS reflect the variety of possible underlying causes (e.g. bacterial infection, inflammation and/or neurological damage) 7, 8. Table 2 3, 4, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44 summarises the range of potential presenting symptoms, based on evidence from the literature and PERG consensus discussions. Symptoms can fluctuate considerably over time 7, 8. The four main domains are urogenital pain, LUTS (voiding or storage symptoms), psychological issues and sexual dysfunction 45.

Table 2

Signs and symptoms reported by patients with CBP and CP/CPPS

Pain symptoms 9, 10, 11, 12, 13, 14 Pain or discomfort in one or multiple urogenital regions including the: • Perineum • Suprapubic region • Testicles, penis (especially penile tip pain) • Lower back, abdomen • Inguinal region/groin • Rectum Pain on urination, or that increases with urination Pain during or after ejaculation Muscle tenderness or dysfunction in abdominal/pelvic regions Neuropathic pain Functional bowel symptoms (e.g. IBS)	Retrospective data indicate that the most prevalent localisation for pain is the perineal region (63% of patients), followed by the testicular, pubic and penile areas 14. Tests for correlations between the NIH-CPSI symptom domains suggest that urogenital pain has a greater impact on QoL than do urinary symptoms 14 IBS has been shown to be present in 22–31% of patients with CBP or CP/CPPS 13, 15 and can increase the severity of pain symptoms 13, 15, 16
Urinary symptoms 9, 11, 17, 18, 19, 20 Voiding LUTS (weak stream, straining and hesitancy) Storage LUTS (urgency ± urge incontinence,	Cohort studies report ≥1 LUTS symptom in 39–68% of patients 17, 18. There may also be an association with recurrent UTIs in a minority of patients 19, 21

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ED, erectile dysfunction; IBS, irritable bowel syndrome; UTI, urinary tract infection.

In order to reflect the evidence base, where some treatments are recommended for use in 'early' and/or 'late' stages of CBP and CP/CPPS, consensus was sought regarding definitions of these stages.

Recommendations

- **Patients can be considered to be (i) in the early stages of the disease if they have experienced persistent, recurrent symptoms for <6 months and are antibiotic-naïve, or (ii) in the later stages of the disease if they have experienced persistent, recurrent symptoms for >6 months and are refractory to initial lines of pharmacotherapy (Level 5).**

Clinical Assessment and Diagnosis

Table 3 11, 20, 38, 40, 46, 47, 48 summarises the investigations and physical examinations that should be considered during initial clinical assessment. Differential diagnosis is important, given the significant overlap of symptoms of CBP and CP/CPPS with those of other conditions 11, 38, 40; investigations to exclude these are detailed in Table 3, with specific recommendations for Prostate Specific Antigen (PSA) testing in Box 2 11, 38, 40, 49.

Box 2

PSA testing recommendations. Adapted from information with the Prostate Cancer Risk Management Programme 49. The Prostate Cancer UK booklet 112 provides relevant patient information for PSA testing

PSA testing should be considered to exclude prostate cancer under the following circumstances:

- Abnormal prostate on DRE
- Symptoms suggest BOO secondary to BPE 11, 38, 40
- Patient concern in relation to prostate cancer

Timing:

PSA testing should be postponed for:

- 6 weeks after treatment for UTI
- 1 week after DRE
- 48 hours after vigorous exercise or sexual activity
- 6 weeks after prostate biopsy
- 2 weeks after flu-like symptoms

Age-specific threshold PSA level measurements for prostate cancer risk management:

- 50–59 years: ≥3.0 ng/mL
- 60–69 years: ≥4.0 ng/mL
- ≥70 years: ≥5.0 ng/mL
- No age-specific ranges for men aged ≥80 years
- Refer to local laboratory upper limits of normal

Treatment effects

- If assessing PSA levels in a patient receiving a 5α-reductase inhibitor, note that a rapid decrease in PSA levels occurs within the first few months of treatment. After 6 months of treatment, PSA will have decreased by ≈50%, setting a new baseline – any subsequent rises from this level should be considered abnormal
- PSA levels may be falsely elevated during an active phase of prostatitis. Avoid testing at these times, if possible, or interpret results with caution

Interpret PSA level results with care

Caution is required with results interpretation, since PSA levels are prostate- rather than cancer-specific and levels can be elevated in/by:

- Prostate enlargement
- Prostate cancer
- Infection or inflammation
- Physical causes – vigorous exercise (e.g. cycling), DRE, prostate biopsy
- A normal prostate

Table 3

Summary of physical examinations and investigations to consider during the clinical assessment of CBP and CP/CPPS

Examinations and investigations*	Setting: Non-specialist	Setting: Specialist	Rating: Core	Rating: Optional	Comments
Physical examinations					
DRE – Including assessment of external genitalia and pelvic floor muscle dysfunction	✓	✓	✓		The bladder may be palpable if there is urinary retention; prostate may be enlarged, tender, or normal. The perineum and superficial pelvic floor muscles may be palpated externally and the deep muscles internally, via the rectum. The quality, timing, strength and endurance of the pelvic floor muscles are tested, in addition to ability to fully relax between contractions. Check that symptoms are not being provoked by other structures
Abdomen – To exclude other causes of abdominal pain	✓	✓	✓		
Urine dipstick and/or MSU for culture/microscopy	✓	✓	✓		To confirm the presence of UTI and/or haematuria 11, 40
Four-glass or two-glass test† VB1 – voided bladder 1: Represents the urethra VB2 – voided bladder 2: Represents the bladder EPS – expressed prostatic secretions: Represents the prostate VB3 – voided bladder 3: Represents the prostate		✓		✓	To evaluate whether there is a bacterial cause, the four-glass (Meares-Stamey) test is considered the 'gold standard' for diagnosis (or exclusion) of CBP, whereby voided bladder (VB) urine (VB1, VB2 and VB3) and EPS samples are taken for culture/microscopy 38, 46. The two-glass test (VB2 and VB3) was shown to offer similar diagnostic sensitivity to the four-glass test 20, while other studies advocate urethral swab plus post-prostatic massage urine analysis (VB3) 47
Tests to exclude differential diagnoses‡					Conditions to be excluded are: urogenital/urological/rectal cancer; prostatic abscess; urinary tract disease (e.g. cystitis, urethritis or upper UTI); urethral
PSA testing to exclude	✓	✓	✓		

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BOO, bladder outlet obstruction; DRE, digital rectal examination; MRI, magnetic resonance imaging; MSU, midstream urine; NAATs, nucleic acid amplification tests; STI, sexually transmitted infection; TRUS, trans-rectal ultrasound; VB, voided bladder. *Based on information adapted from *Map of Medicine. Prostatitis – Primary Care*, January 2014 11; *Map of Medicine. Prostatitis – Secondary Care*, January 2014 38; Nickel et al. 40; and PERG consensus. †Pursued when CBP is suspected. ‡The investigations pursued will depend on symptom presentation and patient history. N.B. Local provider services may vary for the division of assessment options across non-specialist and specialists settings.

A definitive diagnosis of CBP requires the presence of (typically recurrent) UTI and isolation of an aetiologically recognised organism from prostatic fluid or urine 38, 40. There is no 'gold standard' for a definitive diagnosis of CP/CPPS, which is typically based on patient history, symptoms and exclusion of other causes 40. Referral to specialist care should be considered at initial presentation if there is uncertainty regarding the possible differential diagnosis, or if severe symptoms that require immediate specialist attention are present 11.

Tools for evaluation and monitoring Validated symptom-scoring instruments for CBP and CP/CPPS (Table 4) 50, 51 include: the NIH Chronic Prostatitis Symptom Index (NIH-CPSI; evaluating pain, voiding and impact on QoL); the International Prostate Symptom Score (IPSS; urinary symptoms and impact on QoL); and the more recent Urinary, Psychosocial, Organ-specific, Infection, Neurological/systemic, and Tenderness (UPOINT) classification, that aims to stratify patients into specific symptom-led phenotypes 50. The five-item version of the International Index of Erectile Function (IIEF-5) or Sexual Health Inventory for Men (SHIM) specifically evaluate ED.

Table 4

Validated questionnaires for assessment of CBP and CP/CPPS

NIH-CPSI (http://backinmotionpt.com/wp-content/uploads/2010/03/mens_pfcpsi-.pdf)	Nine-item questionnaire (total score 0–43) measuring: • Pain (four questions evaluating pain location, frequency and severity, 0–21) • Voiding (two questions evaluating voiding and storage symptoms, 0–10) • Impact on QoL (three questions, 0–12)
IPSS (http://www.urospec.com/uro/Forms/ipss.pdf)	Eight-item questionnaire measuring: • Urinary symptoms (seven questions evaluating incomplete bladder emptying, frequency, intermittency, urgency, weak stream, straining and nocturia, 0–35) • Impact on QoL (one question, 0–6)
UPOINT [50]	Aims to stratify patients into specific symptom-led phenotypes. Measures urinary symptoms, psychosocial dysfunction, organ-specific findings, infection, neurological/systemic routes, and tenderness of muscles 50 Has been used to inform phenotypically directed multimodal

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Recommendations

- **Reliable instruments, such as the NIH-CPSI, IPSS and UPOINT scales, should be considered to assess initial symptom severity, evaluate phenotypic differences and monitor patients' response to therapeutic intervention (Level 3).**

Psychosocial screening CBP and CP/CPPS can negatively impact QoL 4 and lead to negative behavioural consequences 18, 29, 39, 40, 42. Moreover, men reporting a previous history of sexual, physical or emotional abuse were more likely to have symptoms suggesting CP/CPPS, and previous abuse increased both the NIH-CPSI pain and urinary scores 52. The Delphi approach was used to reach a consensus on the implementation of psychosocial screening.

Recommendations

- **Patients should be screened for psychosocial symptoms (e.g. anxiety or stress) using either the psychosocial yellow flag system and/or Patient Health Questionnaire-9 (PHQ-9) and/or Generalised Anxiety Disorder-7 (GAD-7) scales (Box 3). If a clinically relevant level of psychosocial symptoms is observed, referral to a psychosocial specialist (e.g. psychiatrist, specialist psychologist or cognitive behavioural therapist) should be considered (Level 5).**

Box 3

Psychosocial assessment

Validated questionnaires

- *Patient Health Questionnaire-2 (PHQ-2,* http://www.commonwealthfund.org/usr_doc/PHQ2.pdf) – a two-item questionnaire to assess the frequency of depressed mood over the past 2 weeks
- *Patient Health Questionnaire-9 (PHQ-9,* http://phqscreeners.com/pdfs/02_PHQ-9/English.pdf) – a nine-item questionnaire to assess the frequency of depressed mood over the past 2 weeks
- *Generalised Anxiety Disorder-7 (GAD-7,* http://phqscreeners.com/pdfs/03_GAD-7/English.pdf) – a seven-item questionnaire to assess the severity of generalised anxiety disorder over the past 2 weeks
- *Hospital Anxiety and Depression Scale (HADS)*

Initial presentation questions

Anxiety screening questions: In the last month, have you often been bothered by:

- Feeling nervous, anxious or on edge?
- Not being able to stop or control worrying?

Depression screening questions: In the last month, have you often been bothered by:

- Feeling down, depressed or hopeless?
- Having little interest or pleasure in doing things?

Questions for treatment-refractory patients

Life event screening questions:

- Have you recently undergone any major life events; e.g. moving house, divorce, bereavement or change of job/career?

Trauma and abuse screening questions:

- When growing up, or more recently, have any relationships been difficult or have situations happened that you have found yourself uncomfortable with?

Patient communications It is important that the diagnosis, aetiology and management approaches are discussed with the patient; consensus gained via the Delphi approach recommends the following:

Recommendations (all Level 5)

- **At first presentation, other concerns or differential diagnoses, including urological cancers and infertility, should be discussed with the patient to establish a full patient history and help inform future investigations.**
- **When diagnostic tests for a bacterial cause have been confirmed, the results need to be clearly communicated to the patient, who must be informed of both positive and negative results of diagnostic tests and implications for future treatment.**
- **Patients should be informed of the underlying causes of CBP and CP/CPPS to help improve their understanding. This may include an explanation of basic pelvic anatomy, the chronic pain cycle, and potential routes for pain (neuropathic vs nociceptive).**

Reliable sources for patient information include those available through the Prostate Cancer UK website (Appendix S2).

Treatment Strategies

Table 5 9, 22, 48, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108 summarises the results of the literature search on interventions for CBP or CP/CPPS.

Table 5

Interventions for CBP and CP/CPPS: results of literature search

α-adrenergic antagonists	In all, 10 placebo-controlled RCTs (n = 58–272) were identified that evaluated α-adrenergic antagonists (tamsulosin 53, 54, 55, alfuzosin 56, 57, doxazosin 58, 59, terazosin 60, 61 and silodosin 62) in CBP and CP/CPPS. Most (eight) showed positive results, with significant differences vs placebo in NIH-CPSI total, urinary symptom, pain, and/or QoL scores 54, 55, 56, 57, 59, 60, or in scores using other validated symptom scoring tools 58, 61. However, there was heterogeneity in primary endpoints, patient eligibility criteria (e.g. previous exposure to α-blockers) and trial duration (1.5–6 months). A recent systematic review and network meta-analysis of α-blocker RCTs found significant differences vs placebo in total, pain, voiding and QoL NIH-CPSI scores 63. However, another recent systematic review questioned the clinical significance of these reductions 64. Notably, two of the larger, placebo-controlled trials that evaluated tamsulosin (n = 196) 53 and alfuzosin (n = 272) 57 failed to show any significant difference in total NIH-CPSI scores, the only outcome achieving statistical significance being the score for ejaculation on the Male Sexual Health Questionnaire (P = 0.04) in the alfuzosin trial. Possible reasons include the short treatment duration (≤12 weeks) and/or inclusion of refractory patients with previous exposure to α-blockers 57
Antibiotics	**CBP** Despite the widespread use of antibiotics in patients with CBP and CP/CPPS, evidence in a CBP population primarily exists within RCTs or retrospective comparative trials lacking placebo control. Microbiological eradication rates were 40–77% for ciprofloxacin 65, 66, 67, 75% for levofloxacin 65, 80% for azithromycin 66, 68, 69, 77% for doxycycline 68, 80% for clarithromycin 69, and 62–77% for azithromycin + ciprofloxacin (depending on ciprofloxacin dose) 70. Higher eradication rates (>90%) were reported with azithromycin and levofloxacin either alone, in combination or sequentially, depending on the locality of infection (urethral, prostatic or both) in patients with CBP with *C. trachomatis* infection 71. Significant differences in symptom severity, as assessed by changes in NIH-CPSI scores, were seen between baseline and the end of treatment in two trials 70, 71. Others reported improvements in clinical outcomes but failed to use validated tools to report these 65, 66, 67, 68, 69 Of the identified comparative studies in patients with CBP, one (n = 408) found that levofloxacin offered advantages over ciprofloxacin for bacterial eradication rates and clinical improvement 67, while another of similar size (n = 377) and design showed no significant differences between these agents 65. Azithromycin was reported to be more effective than ciprofloxacin in the treatment of *C. trachomatis* infections 66. Although there is a lack of prospective, head-to-head placebo-controlled trials to assess intraclass and interclass antibiotic comparisons, each class is associated with its own advantages and caveats (Table 6). The quinolones, such as ciprofloxacin and levofloxacin, are considered the antibiotics of choice because of their favourable pharmacokinetic properties 9. Another antibiotic agent, fosfomycin, achieves reasonable intraprostatic tissue levels and is active against extended-spectrum β-lactamase producing organisms; it can be considered in patients with multiresistant Gram-negative infections, based on susceptibility results and discussion with local microbiologists

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RR, relative risk, NSAIDs, non-steroidal anti-inflammatory drugs.

α-adrenergic antagonists ('α blockers') Most of the placebo-controlled RCTs that evaluated α-adrenergic antagonists (tamsulosin, alfuzosin, doxazosin, terazosin and silodosin) in CBP or CP/CPPS found significant reductions in symptoms and/or improvement in QoL scores (Table 5). These findings have contributed to widespread use of these agents in these settings, although their clinical significance has been questioned 64.

Recommendations

- **α-adrenergic antagonists may have a modest treatment effect regarding total, urinary symptom, pain and QoL scores in CBP and CP/CPPS, and should be considered as an initial treatment option (Level 1).**

There is a lack of evidence to inform best practice for the use of these agents and the Delphi panel process was used to reach a consensus.

Recommendations (Level 5)

- **Treatment with α-adrenergic antagonists should be considered in patients who present with significant voiding LUTS (e.g. slow urinary flow, hesitancy).**
- **If no relief from voiding LUTS or other symptoms of CBP or CP/CPPS is achieved within 4–6 weeks, treatment should be stopped and a different pharmacotherapy considered. Patients should be referred to specialist care if other approaches have been exhausted.**
- **Due to the adverse side-effect profiles of this class of drugs, consider offering uroselective α-adrenergic antagonists (e.g. tamsulosin, alfuzosin and silodosin) as first-line treatment in patients with CBP and CP/CPPS who present with voiding LUTS (Level 5).**

Antibiotics A wide spectrum of microbial strains may cause infection in CBP (Box 4) 9. Despite the widespread use of antibiotics in patients with CBP and CP/CPPS, evidence to support their use in these populations is relatively weak. Ciprofloxacin, levofloxacin, azithromycin, doxycycline, and clarithromycin are reported to be effective in eradicating infection and/or improving symptoms in CBP, although there is a lack of prospective, head-to-head placebo-controlled trials to guide choice of agent (Table 5). Table 6 9, 109 summarises key features of the different antibiotic classes. The quinolones (e.g. ciprofloxacin and levofloxacin) are considered the antibiotics of choice because of their favourable pharmacokinetic properties 9.

Box 4

Pathogens implicated in prostatitis. Adapted from Grabe et al. 9

Aetiologically recognised pathogens

Escherichia coli
Klebsiella spp.
Proteus mirabilis
Enterococcus faecalis
Pseudomonas aeruginosa

Organisms of debatable significance

Staphylococci
Streptococci
Corynebacterium spp.
Chlamydia trachomatis
Ureaplasma urealyticum
Mycoplasma hominis

May cause CBP in those with immunodeficiency

Mycobacterium tuberculosis
Candida species
Rare pathogens e.g. Coccidioides immitis, Blastomyces dermatitidis, Histoplasma capsulatum

Table 6

Antibiotic treatment options. Based on information adapted from Grabe et al. 9, the British National

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Common Questions About Chronic Prostatitis. [Am Fam Physician. 2016]
Chronic prostatitis/chronic pelvic pain syndrome: a review of evaluation and therapy. [Prostate Cancer Prostatic Dis....]
Chronic prostatitis: management strategies. [Drugs. 2009]
Non-pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome: a Cochrai [BJU Int. 2019]
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Case Report: Chronic Bacterial Prostatitis Treated With Phage Therapy After Multiple Failed Ar [Frontiers in Pharmacology. 2021]
Therapeutic Applications of Functional Nanomaterials for Prostatitis [Frontiers in Pharmacology. 2021]
Efficacy and Safety of Drug Combinations for Chronic Pelvic Pain: Protocol for a Systematic Review [JMIR Research Protocols. 2021]
A systematic review of cross-cultural adaptation of the National Institutes of Health Chronic Prost [Health and Quality of Life Out...]
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Formulary 109 and PERG expert consensus

Antibiotic	Advantages	Considerations	PERG recommendation
Quinolones: e.g. Ciprofloxacin	Favourable pharmacokinetic profile, with good bioavailability and excellent penetration into prostate. Good activity against typical and atypical pathogens	Drug interactions; Phototoxicity; CNS adverse events (depending on choice of agent), tendonitis	Consider – first-line (Level 5) Dose and duration should be sufficient to eradicate the infection, e.g. ciprofloxacin 500 mg BID × 28 days
Trimethoprim	Active against most relevant pathogens. Monitoring unnecessary. Good penetration into prostate	No activity against *Pseudomonas*, some enterococci and some enterobacteriaceae	Consider – second-line Dose and duration should be sufficient to eradicate the infection, e.g. 200 mg BID × 28 days
Tetracyclines: e.g. Doxycycline	Good activity against *Chlamydia* and *Mycoplasma*	Contraindicated in renal and liver failure. Unreliable activity against coagulase-negative staphylococci, *E. coli*, other enterobacteriaceae, and enterococci. No activity against *P. Aeruginosa*. Risk of skin sensitisation	Consider – second-line Dose and duration should be sufficient to eradicate the infection, e.g. doxycycline 100 mg BID × 28 days
Macrolides: e.g. Azithromycin	Good penetration into prostate Active against *Chlamydia* and Gram-positive bacteria	Minimal supporting data from RCTs. Unreliable activity against Gram-negative bacteria	Reserve for special indications, based on advice from microbiologist and microbiological findings

BID, twice daily (*bis in die*).

Many patients without confirmed infection respond to antibiotic intervention, possibly reflecting an anti-inflammatory or anti-neuropathic effect of the antimicrobial agent. Available evidence indicates that antibiotics can provide symptom improvement in patients with CP/CPPS (Table 5).

Recommendations

- **Antimicrobial therapy may have a moderate effect on total, urinary, pain and QoL scores in CBP and CP/CPPS and should be considered as an initial treatment option (Level 1).**
- **Antimicrobial therapy should be guided by bacterial cultures and sensitivities, taking into consideration any drug interactions and/or contraindications (Level 2).**

With respect to the recommendation of first-line antibiotic intervention, as well as treatment duration/cessation, the consensus of the Delphi panel was as follows (all Level 5):

- **For patients with early-stage CBP and CP/CPPS, offer a quinolone (e.g. ciprofloxacin or ofloxacin) for 4–6 weeks as first-line therapy.**
- **A repeated course of antibiotic therapy (4–6 weeks) should be offered only if a bacterial cause is confirmed or if there is a partial response to the first course.**
- **If a bacterial cause is excluded (e.g. via urine dipstick or culture) and symptoms do not improve after antibiotic therapy, a different treatment method or referral to specialist care should be considered.**

Pain management Published evidence on the use of pharmacotherapy for treatment of pain in CBP and CP/CPPS is scarce (Table 5). Given the link between CP/CPPS and neuropathic pain 39, 78, 110, guidance should be sought from the NICE clinical guideline on the pharmacological management of neuropathic pain 111 if neuropathic pain is suspected. The involvement of, or referral to, a specialist pain team should be sought in such cases. Table 7 109 summarises pharmacotherapy options that may be considered for the treatment of neuropathic pain.

Table 7

Treatment options for neuropathic pain. Based on information from the British National Formulary 109 and PERG expert consensus

Analgesic class	Drug name	Starting dose	Maintenance dose	Common adverse effects	PERG practical points
Gabapentinoids	Gabapentin	100–300 mg at night	600 mg TID	Dizziness, sedation, dyspepsia, dry mouth, ataxia, peripheral oedema, weight gain	(Level 5) Few drug interactions. Safe in overdose. Gut transport mechanism can become saturated, limiting absorption from gastrointestinal tract
	Pregabalin	50–75 mg at night	300 mg BID	Dizziness, sedation, dyspepsia, dry mouth, ataxia, peripheral oedema, weight gain	(Level 5) Linear pharmacokinetics
Tricyclic antidepressants/SNRIs	Amitriptyline	10 mg in evening	50–75 mg in evening	Sedation, dry mouth, blurred vision, urinary retention, constipation, postural hypotension, weight gain	(Level 5) Many patients obtain pain relief at lower dose
	Duloxetine	30 mg in evening (or in morning, if insomnia)	60–120 mg QD	Nausea, sedation, insomnia, headache, dizziness, dry mouth, constipation	(Level 5) Less sedating. May cause insomnia in some patients

BID, twice daily (*bis in die*); QD, once-daily (*quaque die*); SNRI, serotonin-noradrenaline (known in the USA as norepinephrine) reuptake inhibitor; TID, three times daily (*ter in die*).

Due to a lack of published RCT evidence for the use of pain medications in CBP and CP/CPPS, the Delphi panel approach was used to reach a consensus on best practice for the treatment of pain symptoms in the early stages of these conditions.

Recommendations (All Level 5)

- **In patients with early-stage disease who present with pain symptoms, regular paracetamol may be offered.**
- **NSAIDs should be offered only for short-term treatment of pain, to patients with early-stage CBP or CP/CPPS whose symptoms are suspected to be due to an inflammatory process, or those judged to be experiencing an inflammatory flare. These patients should be under regular review by a GP.**
- **To prevent unwanted adverse effects, NSAIDs should be stopped within 4–6 weeks of treatment initiation if they do not reduce symptoms.**
- **In patients with early-stage CBP or CP/CPPS, use of opioids for pain management should be avoided, due to the risk of dependency.**
- **If pain is considered to be neuropathic in origin, treatment with a gabapentinoid (e.g. pregabalin or gabapentin), a tricyclic antidepressant (e.g. amitriptyline, nortriptyline or trimipramine) or a selective serotonin-noradrenaline (known in the USA as norepinephrine) reuptake inhibitor (SNRI; e.g. duloxetine) is warranted (Table 7).**

5α-reductase inhibitors Evidence for the use of 5α-reductase inhibitors in CP/CPPS is very limited. Some improvements in symptomology were noted in small studies with finasteride (Table 5) and also a larger study with dutasteride in older patients with prostatitis-like pain or syndrome who were judged to be at risk of prostate cancer [PSA level of >2.5 ng/mL (aged 50–60 years) or >3.0 ng/mL (aged >60 years)] 82. As noted in the full NICE clinical guidelines for the management of LUTS in men 83, there is a larger body of RCT evidence for use of 5α-reductase inhibitors to treat LUTS in men with BPE (Appendix S2).

Recommendation

- **There is insufficient evidence to warrant recommending 5α-reductase inhibitors as monotherapy in CP/CPPS, unless co-existing BPE is present (Level 2).**

Combined/multimodal therapy Using multiple interventions to target different symptom areas simultaneously may be expected to provide a more beneficial approach than monotherapy. The treatment combination most frequently evaluated has been that of α-blocker and antibiotic therapy. Data are limited, with conflicting findings (Table 5). The Delphi panel approach was, therefore used to reach a consensus.

Recommendation (Delphi panel)

- **Multimodal/combined therapy should be uniquely designed for each individual patient, according to history, physical examination and investigations. Depending on the symptoms at presentation, the following may be considered for adding to first-line antibiotic therapy (all Level 5).**
  - An α-blocker and/or an NSAID.
  - An agent targeting neuropathic pain (e.g. pregabalin).
  - A 5α-reductase inhibitor (predominantly for patients with coexisting LUTS with BPE).

Follow-up and Treatment of Refractory Symptoms

Patients should be followed-up 4–6 weeks after their first presentation. If a bacterial cause has been confirmed, or the patient has had a partial response to antibiotics, a repeat course of antibiotic therapy should be considered. The management strategy should be guided by symptoms.

Recommendations (All Level 5)

- **If a bacterial cause is excluded and no symptom improvement is observed after antibiotic therapy, a different treatment method or referral to specialist care should be considered.**
- **Patients who are refractory to treatment should be questioned about the possibility of any past trauma (including physical, emotional or sexual abuse; questions about abuse should only be implemented if the treating clinician has sufficient skills and resources to manage patients who have experienced abuse).**
- **An MDT approach is recommended, with pharmacotherapy, physical and psychosocial approaches being integrated into a holistic treatment programme individualised for the patient.**
- **The MDT may include urologists, pain specialists, nurse specialists, physiotherapist, GPs, cognitive behavioural/psychological therapists and sexual health specialists.**

Pain management With any pain condition, delayed recovery can lead to chronicity, compromised physical function and development of psychosocial sequelae. If neuropathic pain is suspected, this should be addressed with consideration of pharmacological strategies as already outlined above (Table 7).

Recommendations (PERG)

- **When pain is severe and refractory to the treatments outlined in Table 7, or is significantly impairing the patient's lifestyle and ability to participate in daily activities, referral to a specialist pain service should be considered (Level 5).**

The role of the pain service is to provide a multidisciplinary assessment of the patient and formulate an individualised therapeutic management plan combining treatment of pain, physical disability and psychosocial co-morbidity (Box 5).

Box 5

Pain management services

- Surgical pain interventions; e.g. nerve block procedures. In suitable patients, these can produce temporary or long-term pain relief and, in the context of a physical rehabilitation programme, can enable the patient to progress with physical therapy and rehabilitation
- Education and training in pain management strategies
- Optimisation of analgesic and anti-neuropathic medications
- Intensive and individualised specialist physical therapy or psychology
- Neuromodulation procedures (e.g. spinal cord and sacral nerve root stimulation). Some specialised pain services can provide physiotherapist- or psychologist-led pain management programmes for patients with poor physical function or complex pain problems

Specialist physiotherapy The symptoms of CBP and CP/CPPS may result from physical dysfunction, such as abnormal pelvic muscle spasm and muscle tenderness 10, 12. Therapies that aim to improve relaxation and coordinated use of the pelvic floor muscles, such as biofeedback physical therapy and pelvic floor re-education, as well as myofascial trigger point release, may play a role in providing symptom improvement in patients with CP/CPPS (Table 5). Several studies of acupuncture have provided positive results (Table 5). Transcutaneous electrical nerve stimulation (TENS) 92 was also reported to be beneficial. As most of this evidence is derived from small proof-of-principle or pilot studies, and little is reported on best practice approaches, the Delphi process was used to reach a consensus.

Recommendations (All Level 5)

- **Before referral to specialist physiotherapy, a number of diagnostic tests (e.g. sexually transmitted infection screen, culture/microscopy of voided bladder urine, urethral smear, nucleic acid amplification test and relevant pelvic physical examinations; Table 3) should be conducted to confirm a physical causative route, and exclude non-physical causes, for symptoms.**
- **After referral, a full assessment (e.g. symptom score scaling, examination of the pelvic floor muscles) should be completed to guide the subsequent sequence of physiotherapy treatments.**
- **If the patient presents with psychosocial symptoms, a planned therapeutic strategy involving stress management (including explanation of the chronic pain cycle) should be considered, in addition to seeking advice from the patient's GP or urologist regarding potential onward referral to a psychosocial specialist.**
- **The following specialist physiotherapy treatment options may be considered: pelvic floor re-education; local pelvic floor relaxation; biofeedback; general relaxation; deep relaxation/mindfulness; trigger point release; myofascial release; stretches; exercise for pain management; TENS; acupuncture for trigger point release and pain management; bladder retraining.**

The Delphi panel did not reach a consensus on a number of specialist physiotherapy techniques (core stability training, diaphragmatic breathing exercises, acupuncture for urgency, abdominal massage for constipation, and defaecation techniques), although it was felt that they might be suitable for certain patients, according to symptoms.

Phytotherapy Various phytotherapies, including pollen extracts, bioflavonoids and/or *Serenoa repens* (saw palmetto) have been reported to improve clinical symptoms in small studies in patients with CBP or CP/CPPS (Table 5).

Recommendations

- **Phytotherapy has a modest beneficial effect on symptom improvement in CBP and CP/CPPS and may be considered as a treatment option in treatment-refractory patients (Level 2).**

Cognitive behavioural therapy (CBT) and psychotherapy While it is recognised that psychosocial symptoms may be part of CBP and CP/CPPS 29, 41, 42, 43, no evidence from RCTs or comparative studies is available to support the use of psychological treatment or CBT in these settings. The Delphi process was used to reach a consensus regarding best practice for these techniques.

Recommendations (Level 5)

- **Psychosocial symptoms should be assessed in both the early and late stages of CBP and CP/CPPS. If there is a significant suspicion of psychological factors contributing to a patient's condition, these should be screened for.**
- **CBT should be considered in conjunction with other treatments in later-stage CBP and CP/CPPS, as it may improve pain and QoL.**

Surgical interventions The evidence on surgical management techniques such as prostatectomy, transurethral resection of the prostate (TURP), transrectal high-intensity focused ultrasound (HIFU), transurethral needle ablation (TUNA) of the prostate, and transurethral microwave thermotherapy in CP/CPPS is very limited (Table 5). Repetitive prostatic massage has also been evaluated and the potential usefulness of this technique (with or without a general anaesthetic) in refractory patients was put to the Delphi panel but no consensus was reached. Neuromodulation techniques, such as sacral nerve stimulation 108, have been reported as being successful in treating CP/CPPS but, again, most of this evidence is derived from small proof-of-principle or pilot studies and, to date, little is reported on best practice approaches.

Recommendations

- **There is insufficient evidence to warrant recommending surgical techniques, including radical prostatectomy, TURP, HIFU or prostatic massage for the treatment of CBP or CP/CPPS, except in the context of a clinical trial setting (Level 3).**

Figure 1 provides an algorithm for the diagnosis and management of CBP and CP/CPPS. This summarises the consensus recommendations of the PERG and Delphi panel, as presented above.

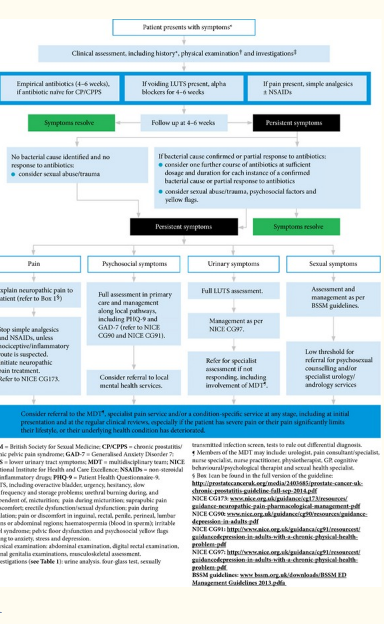

Figure 1

Treatment algorithm for the diagnosis and management of CBP and CP/CPPS. In patients describing typical neuropathic pain symptoms (e.g. 'burning', 'shooting' pain), or in any patient with persistent pain (>3 months), consider the possibility of neuropathic pain and treatment with appropriate anti-neuropathic medication strategies.

Discussion

Go to:

We have developed consensus guidelines aimed at improving the diagnosis and management of CBP and CP/CPPS. Full and 'quick reference' versions of the original guidelines are available from the Prostate Cancer UK website (http://prostatecanceruk.org/prostatitisguideline). The quick reference version is also available at http://www.bjuinternational.com/?p=21102. These guidelines were issued in 2014 and will be considered for review in 3 years' time, unless relevant evidence updates suggest otherwise.

Priorities for implementation are listed in Table 8. We conclude that further research is required to evaluate the following:

- Multimodal pharmacotherapy for patients with CP/CPPS who are refractory to initial mono-pharmacotherapy approaches.
- 5α-reductase inhibitors in CP/CPPS, especially in older patients (aged >50 years) and/or those at increased risk of prostate cancer (aged 50–60 years with PSA levels of >2.5 ng/mL or aged >60 years with PSA level of >3.0 ng/mL).
- The cost impact and effectiveness of interventions to treat CBP and CPPS.
- The effectiveness of a multidisciplinary approach and symptom-based management vs 'usual care' for patients with CBP and CP/CPPS.
- Phosphodiesterase type 5 (PDE5) inhibitors for those with sexual dysfunction.
- The prevalence and impact of psychosocial issues and other co-morbidities e.g. irritable bowel syndrome (IBS).

Table 8

Priorities for management of CBP and CP/CPPS

Patients should be managed according to their individual symptom pattern – no single management pathway is suitable for all patients
Repeated use of antibiotics, such as quinolones, should be avoided where no obvious benefit from infection control is evident or cultures do not support an infective cause
Early use of medication targeting neuropathic pain should be considered for all patients who are refractory to initial treatments. If neuropathic pain is suspected, ensure a prompt referral to an MDT that includes pain specialists
Early referral to specialist services should be considered when patients fail to respond to initial measures
An MDT approach should be implemented, including urologists, pain specialists, nurse specialists, specialist physiotherapists, GPs, cognitive behavioural therapists/psychologists and sexual health specialists
Patients should be fully informed about possible underlying causes and treatment options

Conflicts of Interest

Go to:

Prostate Cancer UK funded the project and guideline development. The funding that Prostate Cancer UK receives from pharmaceutical and medical device companies does not exceed 5% of its total annual income and was not used for the development of this guideline. Hayward Medical Communications received funding from Prostate Cancer UK to manage the literature review, web-based Delphi process and development of the original guideline. Julia Balfour received Prostate Cancer UK funding for editorial support. All PERG members and Delphi panel members participated in the process on a voluntarily basis. Jon Rees (PERG chair) has conducted consultancy work for, and received speaker fees from, Prostate Cancer UK for providing GP medical education classes. All other PERG members declared no conflicts of interest.

Abbreviations

BOO bladder outlet obstruction
BPE benign prostatic enlargement
BSSM British Society for Sexual Medicine
CBP chronic bacterial prostatitis
CBT Cognitive behavioural therapy
CP/CPPS chronic prostatitis/chronic pelvic pain syndrome
DRE digital rectal examination
EAU European Association of Urology
ED erectile dysfunction
EPS expressed prostatic secretions
GAD-7 Generalised Anxiety Disorder-7
IBS irritable bowel syndrome
HIFU high-intensity focused ultrasound
IIEF-5 International Index of Erectile Function
LUTS lower urinary tract symptoms
MDT multidisciplinary team
MRI magnetic resonance imaging
MSU midstream urine
NAATs nucleic acid amplification tests
NICE National Institute for Health and Care Excellence
NIH National Institutes of Health (USA)
NIH-CPSI NIH Chronic Prostatitis Symptom Index
NSAID non-steroidal anti-inflammatory drugs
OCEBM Oxford Centre for Evidence-based Medicine
PDE5 phosphodiesterase type 5
PERG Prostatitis Expert Reference Group
PHQ Patient Health Questionnaire
QoL quality of life
PSA prostate specific antigen
RCT randomised controlled trial
SHIM Sexual Health Inventory for Men
SNRI serotonin-norepinephrine reuptake inhibitor
STI sexually transmitted infection
TENS transcutaneous electrical nerve stimulation
TUNA transurethral needle ablation
TURP transurethral resection of the prostate
UPOINT Urinary, Psychosocial, Organ-specific, Infection, Neurological/systemic, and Tenderness
UTI urinary tract infection
VB voided bladder

Supporting information

Go to:

Appendix S1 Prostatitis Expert Reference Group Members.

Appendix S2 Guidelines and patient information.

Appendix S3 Literature review protocol.

Click here for additional data file. (35K, docx)

Appendix S4 Chronic prostatitis/chronic pelvic pain Delphi survey.

Click here for additional data file. (429K, pdf)

Acknowledgements

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